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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/484,337	06/07/95	BRENNER	M 65850-105-4

EXAMINER

HM11/0304

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ART UNIT	PAPER NUMBER
1646	18

DATE MAILED: 03/04/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on Amdt of 11-28-97

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 22-75 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 22-75 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 16, dated 2-3-98
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Part III: Detailed Office Action

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1646 Technology Center 1600.

2. Any objections, rejections, and/or concerns not herein restated have been withdrawn. The new title is acceptable.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections and Rejections under 35 U.S.C. §112

4. Claims 35 and 70-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 is indefinite and confusing because the following phrase appears to be incomplete or is improperly stated: "...fragment thereof except at the position of none-naturally-occurring cysteine," clarification or correction is requested.

Claims 70-72 are indefinite because the preamble refers to a method of preparing a TNF inhibitory polypeptide as from claim 52, however, the method steps recited in claims 70-72 are not specific steps to preparing the polypeptide, but rather are processes for the **further modification** of the protein after it has been produced. Furthermore, such method steps in claims represent an invention that would be patentably distinct from the method of claim 52, therefore these claims should be deleted, because they appear to be an attempt to have the originally elected invention to be expanded to cover additional inventive concepts. Accordingly, these claims should be deleted.

5. Applicant's arguments filed 11-28-97 have been fully considered but they are not persuasive. See the various arguments following each of the rejections below.

6. Claims 23, 29-30, 31, 32-35, 43, 44-73 and 74-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the full length, precursor forms and

to certain mutants of the 30 kD and 40 kD TNF inhibitor, does not reasonably provide enablement for: a) "fragments of the encoded TNF inhibitory protein as previously set forth and as discussed below (claims 23, 20-30, 32-35, 43-75); b) nor is there enablement for TNF inhibitors with non-naturally occurring cysteine at the C- or N-terminal or at glycosylation sites (claims 31-35 and 43). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Portions of this scope rejection have been withdrawn as a result of the amendment to the claims and newly added claims. The following aspect of this scope rejection are maintained for the reasons set forth in the previous office action. The above stated issue referred to as "b" for enablement of protein with N or C-terminal Cys residues, claims 31-35 and 43 are maintained as of record. The issues above referred to as "a"" for fragments of the 30 or 40 kD protein, claims 23, 20-30, 32-35, 43-75 are also maintained of record.

Most of applicants response represented a re-iteration of the Examiner's previous rejection. Relative to issues "a", applicant's position that the Examiner has not addressed the factors for her conclusion of undue experimentation, nor cited authority to further support such appears to be in error, because this issue was fully developed in the previous office action. For all the reasons previously state, routine screening would not provide sufficient enablement or guidance to enable the full scope of these claims. While it is true that unpredictability alone is not the sole basis for establishing undue experimentation, it is a substantial aspect for the basis of this rejection. Further, in addition to undue experimentation via unpredictability, the previous office action offers additional evidence to show that the artisan would be faced with undue experimentation in a effort to enable the full scope of the claims. This is further complicated by the fact that these claims fail to recite a specific biological activity that the fragment or portion must possess. But, even if an activity was recited or associated with the claims to fragments or portions, the mere recitation of a biological activity, in the absence of other characterization, would not enabled the breadth of these claims.

With regard to issue "b", while the claims have been amended to more clearly define the intent as previously discussed of record (last office action and the interview of 7-17-97, the claims are still broader than the supporting disclose because they encompass C- or N- terminal Cys on the peptide that are not naturally occurring. However, the specification is only enabling for fragments or cleavage that results from the protein at a naturally occurring Cys. The claims read on any TNF inhibitor that has a Cys added at any length on the TNF inhibitor where the Cys is located at the C- or N- or both the C and N-terminal of the protein. The impact and nature of proteins/polypeptides with these Cys terminal units is not clear nor enabled by the specification, nor has applicants provided enablement of guidance that these various C or N-terminal Cys-containing TNF inhibitory protein will possess the desired properties. Amending the claims to state that the Cys is a naturally occurring Cys at the C or N terminal would obviate this aspect of the rejection. The statement at 3rd line of the 2nd paragraph on page 10 of the amendment is not a true assessment of the previous interview. Further, applicants did not provide the documentation and/or declaration pursuant to the interview summary.

Rejections Over Prior Art:

7. Claims 22-69 & 73-75 are rejected under 35 U.S.C. 103(a) as obvious over Wallach et al (EP '378) **or to newly cited Wallach et al ('953).**

Since all of the claims are directed to DNA sequences or the encoded amino acids sequences of the Figures, or to the cys-modifications, or amino acids fragments of the sequences of the figure, this prior art does not anticipate the claims because the prior art does not expressly disclose any DNA/nucleic acids sequences per se. However, the instant claims to these DNA, vectors, and host cells do render the claims prima facie obvious based on the following teachings.

The teachings for Wallach et al (EP '378) have been set forth of record in the previous office actions. The prior art to newly cited Wallach et al (953) discloses a highly purified TNF inhibitory protein that is the same as that disclosed despite the fact that the protein is referred to by slightly different names, and the instant claims recite additional characteristics of the encoded protein, and teach the production of functional derivative and active fragments (see col 2, and the

partial sequence at col 3-4, and col 4-5). Based on all of the identifying characteristic (both physical features and factional features at col 5-7), the prior art encoded protein is that same as that of the instant claims, and any properties recited by the instant claims that define the DNA in terms of the encoded amino acid sequence for the protein that are not recited in the prior art merely represent further characterization of the protein, wherein such properties are inherent to the protein (In re Swinehart, 169 USPQ 226). Since the DNA in claims 23-35, 74-74 and portions of claims 43-73 is defined in terms of the amino acid for the encoded TNF inhibitors , it is well known that the amino acid sequence is inherent to the protein, and based on the partial sequence provided by the prior art at col 3-4, the skilled artisan would have reasonably expected that the encoded protein are the same, in the absence of the prior art to expressly recited the entire amino acid sequence as in Figures 19, 21, 37 & 38)

The above statements have established that the encoded protein defined by the claims and the prior art are the same, and although all of the instant claims are directed to DNA, vectors host cells and recombinant methods of making the protein or host cells, these claims are still considered prima facie obvious despite the fact that the prior art fails to expressly disclose the entire nucleic acid sequence of the TNF inhibitory protein. However, in the express absence of the prior art to recite the actual nucleic acids sequence that encodes for the TNF inhibitor as recited in some of the claims, the prior art provides specific teachings at section 4, col's 10-15 that would enable the skilled artisan to obtain any DNA sequence that would encode for a protein that is the same as that claimed. In further support of this rejection, it is also known that because of codon degeneracy, different nucleic acid sequence can encode for the same protein, but these different nucleic acids do not make the resulting protein per se different. Alternatively, based on codon bias, the specific nucleic acid of applicant's claims that would encode for a protein that has the same physical and functional characteristic would also have been prima facie obvious from all of the teachings of the prior art, because the encoded protein per se is the same irrespective of the different methods in which the prior art and instant application prepared them, and irrespective of the different nucleic acids that would encode for the protein. The preparation of certain mutants,

as well as certain fragments and portions is prima facie obvious from the teachings at col. 4, 11-13 and 16.

Relative to the previously relied upon citation to Wallach et al (EP `378 of 3/89), applicants have argued that the claims are neither anticipated nor obvious from this art based on the manner in which they are prepared from host cell and the resulting glycosylation pattern, and because the prior art to Wallach (`378) does not provide a teaching for the DNA to support a prima facie case of obviousness for a recombinantly-produced protein (it is assumed that applicants may also take this position relative to the newly cited Wallach et al ('953) since this patent is substantially equivalent to the EP document of this rejection). However, applicants have not presented any evidence, inclusive of comparative evidence to show the encoded protein to be patentably distinct, nor that the specific teaching and guidance provided at col 10-15 of Wallach et al (`953), in conjunction with the disclosure of an assay to measure and ensure that the encoded protein possessed the desired activity, would not have rendered the instant DNA claims prima facie obvious. Further, the skilled artisan would not have expected the encoded protein to be functionally distinct based on the absence or presence of the glycosylation-consistent with what has been establish for many protein that are expressed in eukaryotic host to produce a non-glycosylated protein. (See Ex parte Gray 10 USPQ 2d 1922 for support). But most importantly, as stated above in the express absence of the prior art to recite/disclose the actual nucleic acids sequence that encodes for the TNF inhibitor as recited in some of the claims, the prior art provides specific teachings at section 4, col's 10-15 that would enable the skilled artisan to obtain any DNA sequence that would encode for a protein that is the same as that claimed. Alternatively, based on codon bias, the specific nucleic acid of applicant's claims that would encode for a protein that has the same physical and functional characteristic would also have been prima facie obvious from all of the teachings of the prior art, because the encoded protein per se is the same irrespective of the different methods in which the prior art and instant application prepared them, and irrespective of the different nucleic acids that would encode for the protein.

Further argued is that the prior art does not render the claims obvious based on the court's

findings in In re Deuel, which held that the knowledge of a protein, even if partially sequenced, does not render obvious the DNA. However, the instant rejection is distinct and distinguishable over Deuel because contrary to the rejection in Deuel, the instant prior art not only discloses the partial sequence of the protein, but further provides specific teaching and guidance for cloning and expressing the TNF inhibitory protein. These teachings are in the form of a reproducible assay for determining the specific activity of the protein (col 6-7); specific methods for cloning the protein (col 11); methods for preparing a cDNA (col 11); determining the desired DNA sequence based on degeneracy of the genetic code to obtain more than one DNA sequence that would encode for the protein (col 12); obtaining the appropriate oligonucleotides and hybridization techniques to obtain the desired DNA sequence (col 12-13); the selection of appropriate, **as well as preferred**, promoters, vectors and various prokaryotic or eukaryotic host cells for the expression of the protein (col 13-14); and the subsequent purification of the encoded protein after expression (col 15.).

8. Claims 70-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Wallach et al as applied to claims 22-69 and 73-75 above, and further in view of Hiratani ('546), Nishimura et al ('316), Davis et al ('337) or Yamasaki et al.

The disclosure of the primary reference has been set forth above.
although the prior art teach the preparation of functional derivative of the TNF inhibitory protein (col 4), not specifically taught by the primary references is the formulation of the TNF inhibitors as polymer (PEG) conjugates wherein such conjugation provides various enhanced benefits for therapeutic use. EACH of the secondary references provide a wide variety of teaching for conjugating various proteins to polymer conjugates for enhanced bioavailibility and to enhance other properties of the protein when used therapeutically.

No one prior art individually disclose each aspect of the invention, however, at the time of the invention it would have been prima facie obvious to use the teachings of the secondary references and conjugate polymers to the instantly claimed TNF inhibitors of the primary reference because these secondary references teach the advantage of formulating polymers to

different proteins in orders to achieve a number of advantages from such protein therapy. Furthermore, each of the primary references teach that the TNF inhibitors could be formulated in a number of ways conventionally known in the art for use therapeutically, wherein such formulation, while not expressly teaching the conjugation to polymers, include forms that would be representative of the PEG conjugates. Therefore, the skilled artisan would have been motivated by the combined teachings of both the primary and secondary reference for conjugating the TNF inhibitors of the primary reference to the various polymers of the secondary reference, and would have reasonably expected that such conjugation would have provided an additional benefit form use therapeutically.

9. At page 19 applicants provided statement about the various copending application to Brewer et al and Hamptmann et al. Contrary to applicants position these claims do not claim totally distinct subject matter. Thus, in many instances the claims overlap in scope. Since the applications by these two inventive entities were not commonly assigned at the time of filing, Double Patenting rejections can not apply herein. Thus, applicants must present claims to these two inventive entities that do not overlap if patentably distinct claims are sought in each of these applications.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Advisory Information:

11. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to **Garnette D. Draper, Art Unit 1646, whose telephone number is (703) 308-4232.** Examiner Draper can normally be reached Monday through Friday, 9:30 A.M. to 6:00 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED** so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.

PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

GARNETTE D. DRAPER
PRIMARY EXAMINER
GROUP 1800